REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 1-11, the currently pending claims. Claims 12-18 have been canceled, without prejudice to refiling. Claim 1 has been amended. No new matter is added.

Claims 1-6 have been rejected as indefinite in the recitation "a substantially pure population". Without conceding to the correctness of the rejection, Claim 1 has been amended, as the term "substantially pure" was redundant in view of the later recitation of "at least 95%". Withdrawal of the rejection is requested.

Claim 3 has been rejected as indefinite in the recitation of the term "blast cell". Applicants respectfully submit that the term "blast cell" is both well known in the hematological arts, and is described in the application. The Online Medical Dictionary[1], defines blast cell as "an immature cell of a proliferative compartment in a cell lineage that normally represent up to 5% of the cells in the bone marrow". The specification further discusses the blast cell aspect as:

> The subject cells are large, blast cells, therefore an initial separation may select for large cells by various methods known in the art, including elutriation, Ficoll-Hypaque or flow cytometry using the parameters of forward and obtuse scatter to gate for blast cells. A high proportion of the cells are in the mitotic cycle, and vital DNA stains, such as Hoechst 33842 and the like, can be used for separation. (specification, page 9, lines 23-27)

Therefore, it is clear that the recitation of the term "blast cell" refers to large cells that are mitotically active. These properties are useful in the selection of cells. Applicants respectfully submit that the claim language is clear. Withdrawal of the rejection is requested.

Claims 7-11 have been rejected as vague and indefinite in the recitation of a "selecting step". Applicants respectfully submit that the claims clearly state the intended subject matter. The claim states that a population of cells is combined with " reagents that specifically recognize *c-kit,* IL-7Rα and lin markers", and that the cells are then selected for cells that are positive or negative for the markers, as appropriate.

One of skill in the hematologic arts would understand that one of the widely used methods of selection based on affinity chromatography could be used to separate cells that express, or lack expression, of a specific marker. As stated in the specification:

> Separation of the subject cell population will then use affinity separation to provide a substantially pure population. Techniques for affinity separation may include magnetic separation, using antibody-coated magnetic beads, affinity chromatography, cytotoxic agents

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joined to a monoclonal antibody or used in conjunction with a monoclonal antibody, e.g. complement and cytotoxins, and "panning" with antibody attached to a solid matrix, eg. plate, or other convenient technique. Techniques providing accurate separation include fluorescence activated cell sorters, which can have varying degrees of sophistication, such as multiple color channels, low angle and obtuse light scattering detecting channels, impedance channels, etc. The cells may be selected against dead cells by employing dyes associated with dead cells (propidium iodide, LDS). Any technique may be employed which is not unduly detrimental to the viability of the selected cells. (specification on page 9, line 28 to page 10, line 10)

One may use any one of the well known separation techniques, such as flow cytometry, panning, magnetic bead selection, and the like, to select for the cells of interest. The specification further describes detailed methods for binding antibodies, setting gates for flow cytometry, and the like (see specification, pages 10 to 11). Applicants respectfully submit the claims meet the requirements of 35 U.S.C. 112, second paragraph. Withdrawal of the rejection is requested.

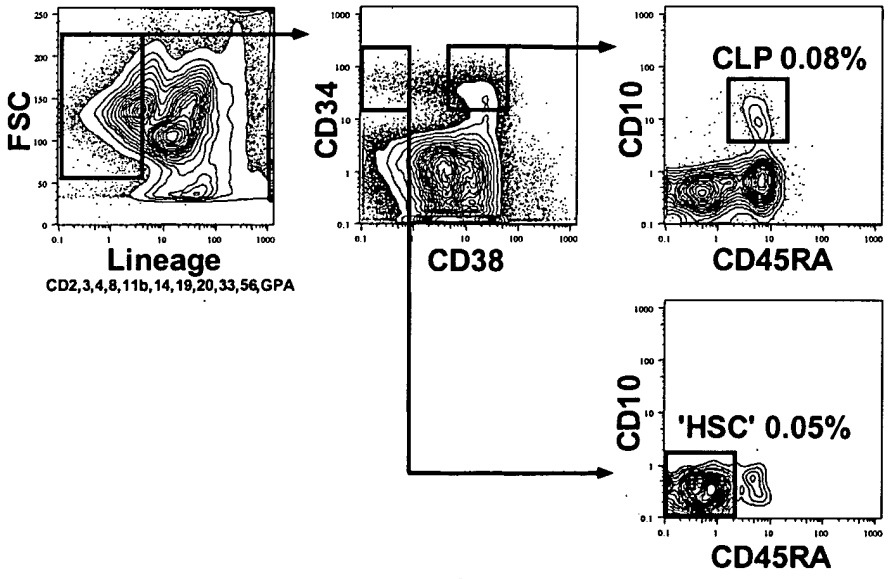
Claims 1-3 and 6-10 have been rejected under 35 U.S.C. 103 as unpatentable over Galy, U.S. Patent no. 5,972,627, Moore et al. (1995) Blood 86:1850-1860, in view of Galy *et al.* (1995) Immunity 3:459-473. Applicants respectfully submit that the presently claimed cell composition and methods are not taught or suggested by Galy.

Galy et al. teaches a population of hematopoietic progenitor cells that are heterogenous in expression of the IL-7 receptor. An analysis of the Galy population is shown below, where whole bone marrow is sorted for expression of lineage markers, CD34, CD10 and CD45RA.

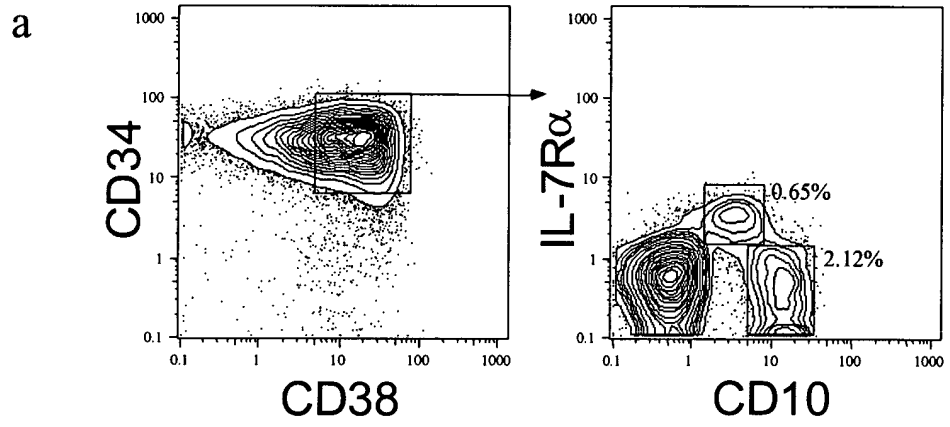
Human lymphoid committed progenitors (CLP)

A. Galy et al., Immunity 1995; 3:459-473)

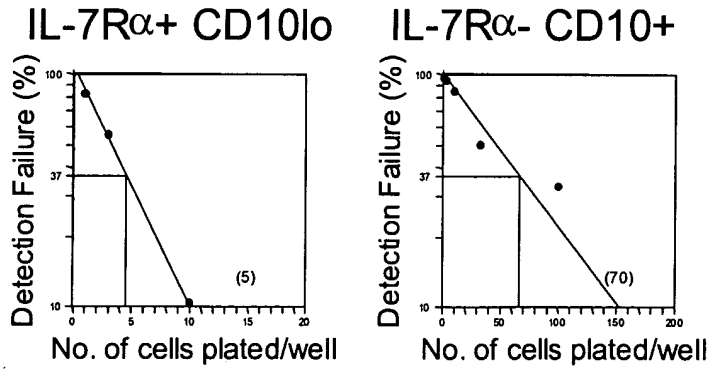
whole bone marrow



The population of cells from the middle plot ($CD34^+CD38^+$) above were analyzed for expression of IL-7Rα. The small population of cells that are CD10 positive (which is coincident with expression of CD45RA as shown above) is heterogenous in expression of IL-7Rα, as shown below, being approximately 25% IL-7Rα positive and 75% negative. In fact, a stringent selection for CD10 positive cells could easily exclude the $IL\text{-}7R\alpha^+$ population, as these cells only weakly express CD10 (for example, see the plot shown in Figure 4 of Galy for CD10 gating).



The expression of IL-7Rα is important for the activity of the cells, as shown by a limiting dilution analysis:



Note the difference in values at the *x* axis, resulting in a clonogenic frequency of 5, rather than 70.

Applicants respectfully submit that Galy *et al.* does not teach one of skill in the art to select a common lymphoid progenitor cell as set forth in the present claims. The expression of IL-7Rα is an important element in the phenotype of the cells.

The secondary reference, Moore *et al.*, does not remedy the deficiencies of the primary reference. Moore *et al.* teach a population of cells that is $CD4^{lo}$. In contrast, the cell population identified by Applicants, as is the Galy population, is selected for lack of expression of CD4, which is

provided in the lineage panel. The cells identified and claimed by Applicants are negative for a marker that is expressed on the Moore *et al.* cells. Therefore two cell populations are clearly different, and mutually exclusive. Further, it can be seen from Figure 1 that the Moore *et al.* cells express quite high levels of c-kit (lower left panel), while the cells of the present invention express very low levels of c-kit (shown in Figure 1C of the present application). One of skill in the art would have no reason to select the population of Galy *et al.* to provide a pure population of IL-7Rα cells, because the cells that express IL-7Rα in Moore et al. differ significantly in their phenotype, and thus are a different population.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 1-4 and 6-11 have been rejected under 35 U.S.C. 103 as being unpatentable over Galy, Moore and Galy *et al.*, as applied above, further in view of Kawamoto *et al.* Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references.

As discussed above, the Galy and Moore et al. references fail to teach the presently claimed invention. The teachings of Kawamoto *et al.* fail to remedy the deficiency. The abstract of Kawamoto *et al.* states that single cells of lineage marker (Lin)-c-kit+Sca-1+ (Sca-1+) and Lin-c-kit+Sca-1-(Sca-1-) populations were taken from the fetal liver. All progenitors in the Sca-1$^-$ population were shown to be committed to generate only T, B or M cells. On the other hand, multipotent progenitors, which are capable of generating T, B and M cells, as well as unipotent progenitors committed to the T, B or M lineage were found in the Sca-1$^+$ population. Bipotent progenitors generating M and T cells and those generating M and B cells were also found in the Sca-1+ population, which probably represent progenitors in the process of commitment. **However, no bipotent progenitors generating T and B cells were detected**. (emphasis added). Therefore, in the Sca-1$^+$ fraction detected by Kawamoto, no cells were found which were capable of giving rise to both lymphoid cell lineages, but which did not give rise to myeloid cell lineages.

Kawamoto therefore teaches away from the cell population taught be Applicants, which gives rise to B and T cells, but not to myeloid cells. In view of the above remarks, withdrawal of the rejection is requested.

Claims 1-3, 5 and 6-10 have been rejected under 35 U.S.C. 103 as being unpatentable over Galy, Moore *et al.* and Galy *et al.*, as applied above, and further in view of Kincade *et al.* and Ballas *et al.* Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references, for the reasons described above. Teachings relating to B

lymphocyte precursors refer to a different population of cells than that taught by Applicants, as the cells of the present invention are not restricted to the B cell lineage, but can give rise to T cells as well.

In view of the above remarks, withdrawal of the rejection is requested.

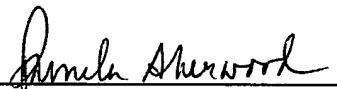
CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number STAN-064.

Respectfully submitted,

Date: March 10, 2003

By: 
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